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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,300	09/13/2001	Helmut Eckert	0147-0229P	2392

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
YAEN, CHRISTOPHER H	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,300	ECKERT ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-9 and 12-14* is/are rejected.

7)☒ Claim(s) *4,5 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/8/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RE: Eckert *et al*
Priority Date: 13 January 1999

1. The finality of the rejection of the last Office action is withdrawn in view of new arguments presented herein.

2. The amendment filed after final on 11/04/2003 is acknowledged and entered into the record. Accordingly, claim 11 is canceled.

3. Claims 1-10 and 12-14 are pending and examined on the merits.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

5. The Information Disclosure Statement filed 12/8/2003 is acknowledged and considered. A signed copy of the IDS is attached hereto.

New Arguments

Claim Rejections - 35 USC § 112, 1st paragraph

6. Claims 1-3, 6-9, and 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising an HE2 anti-EP-CAM antibody or an mmAb 17-1A antibody (as disclosed by Ragnhammar *et al* Cancer Immunol Immunother 1995;40:367-375) and a method of treating epithelial based cancers comprising the administration of the HE2 antibody or

mmAb17-1A antibody, does not reasonably provide enablement for a pharmaceutical composition comprising any and all anti-EP-CAM antibodies and a method of treating all cancers comprising the administration of any and all anti-EP-CAM antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn to 1) a pharmaceutical composition comprising an anti-EP-CAM antibody and a vaccine adjuvant; and 2) a method of treating cancer comprising the administration of the said pharmaceutical composition. The specification teaches the construction of a specific antibody termed HE2 when administered to a subject induces the production of antibodies directed against the EP-CAM cell surface antigen (see page 11) – i.e. anti-idiotypic antibody responses. The art teaches that another antibody mmAb 17-1A which is directed to an antigen termed 17-1A, (also known as EP-CAM, as evidenced by Balzar *et al* J. Mol Med 1999;77:699-712) when administered to a patient is effective also effective in the induction of an anti-idiotypic antibody response (see abstract). The specification also describes a method of treating tumor cells that are of epithelial cell origin, such as lung carcinoma cells (see page 13) and stomach cancer cells (see page 14). However, the specification fails to provide enabling disclosure with regard to using or making any other type of anti-EP-CAM antibody nor does it teach a method of treating cancers other than carcinomas, such as blood cancers or cancers of endothelial cell origin.

The art teaches that the process of generating internal image anti-idiotype antibodies are well known to those of skill in the art and can result in the production of internal image antibodies that mimic the immunological properties of the initial antigen (i.e., tumor antigen or infectious agent). For support, see Raychaudhuri S., U.S. Patent 5,270,202, bridging paragraph of columns 2-3). Wu, X-R (U.S. Patent 6,632,431 B2) teaches the three types of anti-idiotypic antibodies, alpha ($Ab_2\alpha$), beta ($Ab_2\beta$) and epsilon ($Ab_2\varepsilon$) and only $Ab_2\beta$, which binds to the CDR can be an internal image of the antigen and has been proposed to be paratropic and to mimic the molecular features of the original antigen (see column 3, lines 44-58). Raychaudhuri S. acknowledges that the successful production of anti-idiotypic antibodies is an unpredictable endeavor (see column 3, lines 35-54). "In short, the discovery of therapeutically useful anti-idiotypic antibodies is as much art as science" (see column 3, lines 49-51). Chatterjee et al (U.S. Patent 6,235,280 B1) teach that not all anti-idiotype antibodies can be used in therapeutic regimens against tumors. First, only a fraction of antibodies raised against an Ab1 (anti-antigen antibody) are limited in their reactivity to the paratope of Ab1 (i.e., are non-reactive against features shared with other potential antibodies in the host). Second, anti-idiotype antibodies are not necessarily immunogenic. Third, only a fraction of the immunogenic anti-idiotypes elicit an antigen-specific immune response. Further, anti-idiotype therapy with respect to tumor origin and antigens expressed should be evaluated on a case-by-case basis since different cancers have widely varying molecular and clinical characteristics (see column 2, lines 39-53).

The art also teaches that the cellular antigen EP-CAM is a pan carcinoma marker or an antigen that is expressed by the majority of epithelial neoplasias (see Balzar *et al* J. Mol Med 1999;77:699-712). However, no art of record teaches that this antigen is expressed on any other cell type other than epithelial cells and or cancer cells of epithelial cell origin and hence no record of this tumor antigen can be found in hematopoietic or endothelial cells or their corresponding tumors. As such, the administration of an antibody against EP-CAM would be unpredictable in its effectiveness in treating a cancer, because neither the specification nor the prior art teach such a treatment. Furthermore, the art teaches that the treatment of cancer in general is at most unpredictable as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Because the specification has only taught a single antibody, HE2, that is capable of inducing the production of antibodies to EP-CAM in vivo and because there is a lack of guidance with regard to methods for treating cancers other than those of epithelial cell origin, one of skill in the art cannot make a reasonable correlation between what is

taught in the specification to what is being broadly claimed. The specification lacks working examples that teach one of skill in the art the necessary steps or requirements for the treatment of any and all cancers (with the exception of carcinoma) and whether other antibodies or fragments of antibodies directed against EP-CAM would function in a manner similar to that disclosed in the specification (i.e. induce the formation of antibodies against the TAA EP-CAM) for the only disclosed antibody, HE2.

Therefore, given the unpredictability in the art with regards to the manufacturing of anti-idiotypic antibodies, the lack of evidence and teaching of anti-EP-CAM antibodies in treating cancers other than carcinomas, the unpredictability of the field, in general, and absent sufficient teachings in the specification to overcome the teachings of unpredictability found in the art, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

7. Claims 1-3, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Ragnhammar *et al* (Cancer Immunol. Immunother. 1995 June;40(6):367-375).

8. Ragnhammar *et al* teach a pharmaceutical composition comprising an anti 17-1A antibody and GM-CSF. The art also defines 17-1A antigen as EP-CAM (as evidenced by Balzar *et al* J. Mol Med 1999;77:699-712). Because the specification defines an "adjuvants", as biological agents of which include GM-CSF (see page 9), the GM-CSF used by Ragnhammar *et al* falls within the scope of "pharmaceutical adjuvant" as claimed. It is further taught by Ragnhammar *et al* that the antibody is a monoclonal

antibody derived from a mouse. And finally, Ragnhammar *et al* disclose that the composition is useful in the treatment of advanced colorectal carcinoma.

Claim Rejections - 35 USC § 103

9. Claims 1-3, 7,8, 9, 12, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ragnhammar *et al* in view of Ragnhammar *et al* (Med Oncol & Tumor Pharmacother 1993; 10(1/2):61-70).

The teachings of Ragnhammar *et al* (Cancer Immunol. Immunother. 1995 June;40(6):367-375) are set forth above as applied to claims 1-3, and 8. Ragnhammar *et al* (Cancer Immunol. Immunother. 1995 June;40(6):367-375) do not teach the method of treating a carcinoma cancer through the administration of the 17-1A antibody by subcutaneous, intradermal, or intramuscular injection, nor do they teach the administration of the specific dosages of antibody claimed in the instant invention. This deficiency is made up by Ragnhammar *et al* (Med Oncol & Tumor Pharmacother 1993; 10(1/2):61-70).

Ragnhammar *et al* (Med Oncol & Tumor Pharmacother 1993; 10(1/2):61-70) teach the separate administration of a monoclonal 17-1A antibody and GM-CSF, wherein the administration of the 17-1A antibody is accomplished by intradermal injection at a dose range of 1 mg to 4mg (see page 62).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the 17-1A antibody (an EP-CAM antibody) to a patient intradermally at a dose range of 1-4mg because Ragnhammar *et*

al (Med Oncol & Tumor Pharmacother 1993; 10(1/2):61-70) taught that the administration of the antibody was effective in treating colorectal carcinoma. One of skill in the art would have been motivated to combine the references because it would provide one of ordinary skill in the art a reasonable expectation of success in using a lower dosage for a composition for treating carcinomas, wherein the composition can be formulated for intradermal injection into a patient for the treatment of a carcinomas. Although the dose range of 0.5mg was not contemplated or characterized by Ragnhammar *et al* , the claimed dosage of 0.5mg is an obvious variation of the reference teaching absent a showing of unobvious property. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

All other rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in a paper filed 11/04/2003.

Conclusion

10. Claims 4-5 and 10 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
April 29, 2004

GARY NICKOL
PRIMARY EXAMINER